09/617913

What is claimed is:

1. An agent that inhibits one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms.

2. The agent according to claim 1, wherein the agent that inhibits one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms, is an oligonucleotide.

3. The oligonucletide according to claim 2, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA that encodes a portion of one or more histone deacetylase isoforms.

4. The oligonucleotide according to claim 3, wherein the oligonucleotide is a chimeric oligonucleotide.

5. The oligonucleotide according to claim 3, wherein the oligonucleotide is a hybrid oligonucleotide.

6. The oligonucleotide according to claim 3, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA selected from the group consisting of

(a) a nucleic acid molecule encoding a portion of HDAC-1 (SEQ ID NO:2),

(b) a nucleic acid molecule encoding a portion of HDAC-2 (SEQ ID NO:4),

(c) a nucleic acid molecule encoding a portion of HDAC-3 (SEQ ID NO:6),

(d) a nucleic acid molecule encoding a portion of HDAC-4 (SEQ ID NO:8),

(e) a nucleic acid molecule encoding a portion of HDAC-5 (SEQ ID NO:10),

(f) a nucleic acid molecule encoding a portion of HDAC-6 (SEQ ID NO:12),

(g) a nucleic acid molecule encoding a portion of HDAC-7 (SEQ ID NO:14), and

(h) a nucleic acid molecule encoding a portion of HDAC-8 (SEQ ID NO:18).

7. The oligonucleotide according to claim 6 having a nucleotide sequence of from about 13 to about 35 nucleotides.

8. The oligonucleotide according to claim 6 having a nucleotide sequence of from about 15 to about 26 nucleotides.

9. The oligonucleotide according to claim 6 having one or more phosphorothioate internucleoside linkage, being 20-26 nucleotides in length, and being modified such that the terminal four nucleotides at the 5′ end of the oligonucleotide and the terminal four nucleotides at the 3′ end of the oligonucleotide each have 2′ -O-methyl groups attached to their sugar residues.

10. The oligonucleotide according to claim 6, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA encoding a portion of HDAC-1 (SEQ ID NO:2).

11. The oligonucleotide according to claim 10 that is SEQ ID NO:17 or SEQ ID NO:18.

12. The oligonucleotide according to claim 6, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA encoding a portion of HDAC-2 (SEQ ID NO:4).

13. The oligonucleotide according to claim 12 that is SEQ ID NO:20.

14. The oligonucleotide according to claim 6, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA encoding a portion of HDAC-3 (SEQ ID NO:6).

15. The oligonucleotide according to claim 14 that is SEQ ID NO:22.

16. The oligonucleotide according to claim 6, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA encoding a portion of HDAC-4 (SEQ ID NO:8).

17. The oligonucleotide according to claim 16 that is SEQ ID NO:24 or 26.

18. The oligonucleotide according to claim 6, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA encoding a portion of HDAC-5 (SEQ ID NO:10).

19. The oligonucleotide according to claim 18 that is SEQ ID NO:28.

20. The oligonucleotide according to claim 6, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA encoding a portion of HDAC-6 (SEQ ID NO:12).

21. The oligonucleotide according to claim 20 that is SEQ ID NO:29.

22. The oligonucleotide according to claim 6, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA encoding a portion of HDAC-7 (SEQ ID NO:14).

23. The oligonucleotide according to claim 22 that is SEQ ID NO:31.

24. The oligonucleotide according to claim 6, wherein the oligonucleotide is complementary to a region of RNA or double-stranded DNA encoding a portion of HDAC-8 (SEQ ID NO:16).

25. The oligonucleotide according to claim 24 that is SEQ ID NO:32 or SEQ ID NO:33.

26. A method for inhibiting one or more histone deacetylase isoforms in a cell comprising contacting the cell with the agent according to claim 1.

27. A method for inhibiting one or more histone deacetylase isoforms in a cell comprising contacting the cell with the oligonucleotide according to claim 3.

28. The method according to claim 27, wherein cell proliferation is inhibited in the contacted cell.

29. The method according to claim 27, wherein the oligonucleotide that inhibits cell proliferation in a contacted cell induces the contacted cell to undergo growth retardation.

30. The method according to claim 27, wherein the oligonucleotide that inhibits cell proliferation in a contacted cell induces the contacted cell to undergo growth arrest.

31. The method according to claim 27, wherein the oligonucleotide that inhibits cell proliferation in a contacted cell induces the contacted cell to undergo programmed cell death.

32. The method according to claim 27, wherein the oligonucleotide that inhibits cell proliferation in a contacted cell induces the contacted cell to undergo necrotic cell death.

33. The method according to claim 27, further comprising contacting the cell with a histone deacetylase small molecule inhibitor.

34. A method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of the agent of claim 1.

35. A method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of the oligonucleotide of claim 3.

36. The method according to claim 35, wherein the animal is a human.

37. The method according to claim 35, further comprising administering to the animal a therapeutically effective amount of a histone deacetylase small molecule inhibitor with a pharmaceutically acceptable carrier for a therapeutically effective period of time.

38. A method for identifying a histone deacetylase isoform that is required for the induction of cell proliferation, the method comprising contacting the histone deacetylase isoform with an inhibitory agent, wherein a decrease in the induction of cell proliferation indicates that the histone deacetylase isoform is required for the induction of cell proliferation.

39. The method according to claim 38, wherein the inhibitory agent is an oligonucleotide of claim 3.

40. A method for identifying a histone deacetylase isoform that is required for cell proliferation, the method comprising contacting the histone deacetylase isoform with an inhibitory agent, wherein a decrease in cell proliferation indicates that the histone deacetylase isoform is required for cell proliferation.

41. The method according to claim 40, wherein the inhibitory agent is an oligonucleotide of claim 3.

42. A method for identifying a histone deacetylase isoform that is required for the induction of cell differentiation, the method comprising contacting the histone deacetylase isoform with an inhibitory agent, wherein an induction of cell differentiation indicates that the histone deacetylase isoform is required for the induction of cell proliferation.

43. The method according to claim 38, wherein the inhibitory agent is an oligonucleotide of claim 3.

44. A method for inhibiting cell proliferation in a cell, comprising contacting a cell with at least two reagents selected from the group consisting of an antisense oligonucleotide that inhibits a specific histone deacetylase isoform, a histone deacetylase small molecule inhibitor that inhibits a specific histone deacetylase isoform, an antisense oligonucleotide that inhibits a DNA methyltransferase, and a DNA methyltransferase small molecule inhibitor.

45. A method for modulating cell proliferation or differentiation of a cell comprising inhibiting a specific HDAC isoform that is involved in cell proliferation or differentiation by contacting the cell with an agent of claim 1.

46. The method according to claim 45, wherein the cell proliferation is neoplasia.

47. The method according to claim 46, wherein the histone deacetylase isoform is selected from the group consisting of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7 and HDAC-8.

48. The method according to claim 47, wherein the histone deacetylase isoform is HDAC-1 and/or HDAC-4.